PATENT
Atty. Docket No.: 5048P1C1D1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Dixon, *et al.*

SERIAL NO.: Divisional application of U.S.S.N. 09/453,613

FILING DATE: herewith

TITLE: Substituted 2-Arylamino Heterocycles and Compositions Containing Them for Use as Progesterone Receptor Binding Agents

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PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Preliminary Amendment is submitted in the above-captioned divisional application of U.S.S.N. 09/453,613. Please amend the application as follows:

In the Specification

Please amend the specification as shown in the attached page. A marked version of the specification showing the changes made is also attached.

In the Claims

Please cancel claims 4 and 5.

Please amend claims 1-3, 7 and 8, as shown in the attached sheets. A marked version of the claim set showing the changes made is also attached.

Remarks

By way of this Preliminary Amendment, claims 1-3 and 6-9 are pending. Claims 4 and 5 have been canceled, and claims 1-3, 7 and 8 have been amended. These claim cancellations and amendments are being made to cancel unelected subject matter or subject matter allowed in the parent application. No new matter was added by way of these amendments.

Conclusion

Applicants believe that the subject matter of the pending claims is patentable and that the instant application should accordingly be allowed. If the Examiner believes that a conversation with Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned attorney at (203) 812-3964.

Respectfully submitted,

Dated: Oct. 23, 2001

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Amendments to Specification for Attorney Docket Number 5048P1C1D1

On page 1, line 1 of the specification, please insert the following:

---Cross Reference to Related Applications

This application is a divisional of U.S.S.N. 09/453,613, filed December 3, 1999, which claims priority to and the benefit of U.S.S.N. 60/287,573, filed January 14, 1999.--

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Substituted 2-arylimino heterocycles and compositions containing them, for use as progesterone receptor binding agents

> CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional of USSN 09/453,613, filed December 3, 1999, which claims priority to and the benefit of USSN 60/287,573, filed January 14, 1999.

FIELD:

This invention relates to heterocyclic pharmaceuticals, and more particularly, to 2-arylimino heterocycles, pharmaceutical compositions containing them, and their use in modulating progesterone receptor mediated processes.

BACKGROUND:

An agent which binds to the progesterone receptor may be employed for a wide variety of indications, including those shown in the lettered paragraphs below:

A1) to enhance bone formation in bone weakening diseases, for the prevention of and/or treatment of osteopenia or osteoporosis (Manzi, et al., J. Soc. Gynecol. Invest., 1, 302 (1994); Scheven, et al., Biochem. Biophys. Res. Commun., 186, 54 (1992); Verhaar, et al., Bone, 15, 307 (1994); Ontjes, In "Calcium and Phosphorus in Health Diseases", Anderson and Garner (Eds.), CRC Press, 207 (1996); Scheven et al., Biochem. Biophys. Res. Commun., 186, 54 (1992)) including corticosteroid-induced osteoporosis (Picardo, et al., Drug Safety 15, 347 (1996)), postmenopausal osteoporosis, or Paget's disease;

A2) as an agent to enhance fracture healing;

B1) as a female contragestive agent, (Cadepond et al., Annu. Rev. Med., 48, 129 (1997); Heikinheimo Clin. Pharmacokinet., 33, 7 (1997); Li et al., Adv. Contracept., 11, 285 (1995); Spitz et al., Adv. Contracept. 8, 1 (1992); Spitz et al., Annu. Rev. Pharmacol. Toxicol., 36, 47 (1996));

B2) for prevention of endometrial implantation (Cadepond et al., Annu. Rev. Med., 48, 129 (1997));

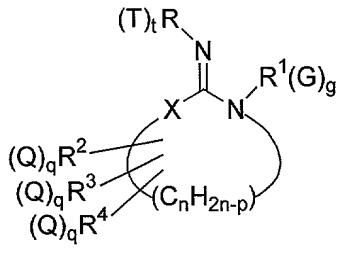
B3) for the induction of labor (Heikinheimo Clin. Pharmacokinet., 33, 7 (1997); Karalis et al., Ann. N. Y. Acad. Sci., 771, 551 (1995)), including the case of foetus mortus (Heikinheimo, Clin. Pharmacokinet., 33, 7 (1997); Cadepond et al., Annu. Rev. Med., 48, 129 (1997));

B4) for treatment of luteal deficiency (Pretzsh et al., Zentralbl. Gynaekol., 119 (Suppl. 2), 25 (1997); Bezer et al., In "Molecular and Cellular Aspects of Periimplantation Processes", Dey (Ed.), Springer-Verlag, p. 27 (1995));

B5) to enhance recognition and maintanence of pregnancy (Bezer et al., In "Molecular and Cellular Aspects of Periimplantation Processes", Dey (Ed.), Springer-Verlag, p. 27 (1995));

Amended Claims for Attorney Docket Number 5048P1C1D1

1. (Amended) A compound having the formula



wherein

R is

substituted aryl of 6 - 14 carbons wherein the substituent is T; or

heteroaryl of 3 - 10 carbons and containing 1 - 3 heteroatoms selected from the group consisting of N, O, and S, with the proviso that R is other than benzofuran or benzothiophene;

R^1 is

alkyl of 1 - 10 carbons;

cycloalkyl of 3 - 12 carbons and containing 1 - 3 rings;

heterocycloalkyl of 4 - 7 carbons and containing 1 - 3 rings and 1 - 3 heteroatoms selected from the group consisting of N, O, and S;

alkenyl of 2 - 10 carbons;

cycloalkenyl of 5 - 12 carbons and containing 1 - 3 rings; or

alkynyl of 3 - 10 carbons;

R^2, R^3, and R^4 are independently selected from the group consisting of

H;

alkyl of 1 - 10 carbons;

cycloalkyl of 3 - 12 carbons;

alkenyl of 2 - 10 carbons;

cycloalkenyl of 5 - 12 carbons;

substituted aryl of 6 - 13 carbons wherein the substituent is Q;

heteroaryl of 3 - 9 carbons and containing 1 - 3 heteroatoms selected from the group consisting of N, O, and S;

CO_2R^5 ; wherein

R^5 is alkyl of 1 - 4 carbons, haloalkyl of 1 - 4 carbons, cycloalkyl of 3 - 6 carbons, or halocycloalkyl of 3 - 6 carbons;

halogen; and

=O , representing two of the groups R^2, R^3, and R^4;

X is O;

n is 2;

p is the sum of non-H substituents R^2, R^3, and R^4;

T is a substituent selected from the group consisting of

alkyl of 1 - 4 carbons;

alkoxy of 1 - 4 carbons;

aryl of 6 - 10 carbons;

CO_2H;

CO_2R^5;

alkenyl of 2 - 4 carbons;

alkynyl of 2 - 4 carbons;

$C(O)C_6H_5$;

$C(O)N(R^6)(R^7)$;wherein

R^6 is H or alkyl of 1 - 5 carbons; and

R^7 is H or alkyl of 1 - 5 carbons;

$S(O)_{y'}R^8$; wherein

y' is 1 or 2; and

R^8 is alkyl of 1 - 5 carbons;

SO_2F;

CHO;

OH;

NO_2;

CN;

halogen;

OCF_3;

N-oxide;

$O\text{-}C(R^9)_2\text{-}O$, the oxygens being connected to adjacent positions on R; and wherein

R^9 is H, halogen, or alkyl of 1 - 4 carbons;

$C(O)NHC(O)$, the carbons being connected to adjacent positions on R; and

$C(O)C_6H_4$, the carbonyl carbon and the ring carbon ortho to the carbonyl being connected to adjacent positions on R;

t is 1 - 5;

provided that when substituent moiety T is alkyl of 1 - 4 carbons, alkoxy of 1 - 4 carbons, aryl of 6 - 10 carbons, CO_2R^5, alkenyl of 2 - 4 carbons, alkynyl of 2 - 4 carbons, $C(O)C_6H_5$, $C(O)N(R^6)(R^7)$, $S(O)_yR^8$, $O\text{-}C(R^9)_2\text{-}O$, or $C(O)C_6H_4$, then T optionally may bear secondary substituents selected from the group consisting of alkyl of 1 - 4 carbons; alkoxy of 1 - 4 carbons; CO_2R^5; CO_2H; $C(O)N(R^6)(R^7)$; CHO; OH; NO_2; CN; halogen; $S(O)yR^8$; or =O, the number of said secondary substituents being 1 or 2

with the exception of halogen, which may be employed up to the perhalo level;

G is a substituent selected from the group consisting of

halogen;

OH;

OR^5;

=O , representing two substituents G;

alkyl of 1 - 4 carbons;

alkenyl of 1 - 4 carbons;

cycloalkyl of 3 - 7 carbons;

heterocycloalkyl of 3 - 5 carbons and 1 - 3 heteroatoms selected from the group consisting of N, O, and S;

cycloalkenyl of 5 - 7 carbons;

heterocycloalkenyl of 4 - 6 carbons and 1 - 3 heteroatoms selected from the group consisting of N, O, and S;

CO_2R^5;

$C(O)N(R^6)(R^7)$;

aryl of 6 - 10 carbons;

heteroaryl of 3 - 9 carbons and 1 - 3 heteroatoms selected from the group consisting of N, O, and S;

NO_2;

CN;

$S(O)_yR^8$;

SO_3R^8; and

$SO_2N(R^6)(R^7)$;

g is 0 - 4, with the exception of halogen, which may be employed up to the perhalo level;

provided that when substituent G is alkyl of 1 - 4 carbons, alkenyl of 1 - 4 carbons, cycloalkyl of 3 - 7 carbons, heterocycloalkyl of 3 - 5 carbons,

cycloalkenyl of 5 - 7 carbons, or heterocycloalkenyl of 4 - 6 carbons, then G optionally may bear secondary substituents of halogen up to the perhalo level; and when substituent G is aryl or heteroaryl, then G optionally may bear secondary substituents independently selected from the group consisting of alkyl of 1 - 4 carbons and halogen, the number of said secondary substituents being up to 3 for alkyl moieties, and up to the perhalo level for halogen;

Q is a substituent selected from the group consisting of

alkyl of 1 - 4 carbons;

haloalkyl of 1 - 4 carbons;

cycloalkyl of 3 - 8 carbons;

alkoxy of 1 - 8 carbons;

alkenyl of 2 - 5 carbons;

cycloalkenyl of 5 - 8 carbons;

aryl of 6 - 10 carbons;

heteroaryl of 3 - 9 carbons and containing 1 - 3 heteroatoms selected from the group consisting of N, O, and S;

CO_2R^5;

=O , representing two substituents Q;

OH;

halogen;

$N(R^6)(R^7)$;

$S(O)_yR^8$;

SO_3R^8; and

$SO_2N(R^6)(R^7)$;

q is 0 - 4

provided that when substituent Q is aryl or heteroaryl, then Q optionally may bear secondary substituents independently selected from the group consisting of alkyl of 1 - 4 carbons and halogen, the number of said secondary substituents being up to 3 for alkyl moieties and up to the perhalo level for halogen; and

with the further provisos that:

a) two of $(Q)_qR^1$, $(Q)_qR^2$, $(Q)_qR^3$, and $(Q)_qR^4$ may be joined, and taken together with the atom(s) to which they are attached, form a spiro or nonspiro nonaromatic ring of 3 - 8 members containing 0 - 2 heteroatoms selected from the group consisting of N, O, and S;

b) at least one of R^2, R^3, and R^4 is other than H;

c) if t = 1, then T is selected from the list of substituents T above excepting alkyl, and the 4-position of the 1,3-oxazolidine ring must bear a substituent;

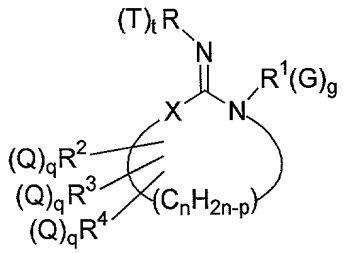
d) the sum of non-hydrogen atoms in R^1, R^2, R^3, and R^4 is at least 5;

e) when the 4-position of the 1,3-oxazolidine ring bears a carbonyl group, and R bears halogen at its 2- and 4- positions, then the 5-position of R bears H;

f) when the 4-position of the1,3-oxazolidine ring may bear a carbonyl only if the 5-position of said ring bears at least one non-H substituent;

and pharmaceutically acceptable salts thereof.

2. (Amended) A compound having the formula



wherein

R is

substituted phenyl wherein the substituent is T; or

substituted pyridyl wherein the substituent is T;

R^1 is

alkyl of 1 - 10 carbons;

cycloalkyl of 3 - 12 carbons and containing 1 - 3 rings;

alkenyl of 2 - 10 carbons;

cycloalkenyl of 5 - 12 carbons and containing 1 - 3 rings; or

alkynyl of 3 - 10 carbons;

R^2, R^3, and R^4 are independently selected from the group consisting of

H;

alkyl of 1 - 10 carbons;

cycloalkyl of 3 - 12 carbons;

alkenyl of 2 - 10 carbons;

cycloalkenyl of 5 - 12 carbons; and

=O , representing two of the groups R^2, R^3, and R^4;

X is O;

n is 2;

p is the sum of non-H substituents R^2, R^3, and R^4;

T is a substituent selected from the group consisting of

alkyl of 1 - 4 carbons;

alkoxy of 1 - 4 carbons;

alkenyl of 2 - 4 carbons;

alkynyl of 2 - 4 carbons;

NO_2;

CN; and

halogen;

t is 1 - 5;

provided that when substituent moiety T is alkyl of 1 - 4 carbons, alkoxy of 1 - 4 carbons, alkenyl of 2 - 4 carbons, or alkynyl of 2 - 4 carbons, then T optionally may bear secondary substituents selected from the group consisting of

alkyl of 1 - 4 carbons;

alkoxy of 1 - 4 carbons;

CO_2R^5; wherein

R^5 is alkyl of 1 - 4 carbons, haloalkyl of 1 - 4 carbons, cycloalkyl of 3 - 6 carbons, or halocycloalkyl of 3 - 6 carbons;

CO_2H;

$C(O)N(R^6)(R^7)$; wherein

R^6 is H or alkyl of 1 - 5 carbons; and

R^7 is H or alkyl of 1 - 5 carbons;

CHO;

OH;

NO_2;

CN;

halogen;

$S(O)yR^8$; wherein

R^8 is alkyl of 1 - 5 carbons; and

=O, representing two secondary substituents;

the number of said secondary substituents being 1 or 2 with the exception of halogen, which may be employed up to the perhalo level;

G is a substituent selected from the group consisting of

halogen;

OR^5;

alkyl of 1 - 4 carbons;

alkenyl of 1 - 4 carbons;

cycloalkyl of 3 - 7 carbons;

cycloalkenyl of 5 - 7 carbons;

aryl of 6 - 10 carbons; and

CN;

g is 0 - 4, with the exception of halogen, which may be employed up to the perhalo level;

provided that when substituent G is alkyl of 1 - 4 carbons, alkenyl of 1 - 4 carbons, cycloalkyl of 3 - 7 carbons, or cycloalkenyl of 5 - 7 carbons, then G optionally may bear secondary substituents of halogen up to the perhalo level; and when substituent G is aryl, then G optionally may bear secondary substituents independently selected from the group consisting of alkyl of 1 - 4 carbons and halogen, the number of said secondary substituents being up to 3 for alkyl moieties, and up to the perhalo level for halogen;

Q is a substituent selected from the group consisting of

alkyl of 1 - 4 carbons;

haloalkyl of 1 - 4 carbons;

cycloalkyl of 3 - 8 carbons;

alkoxy of 1 - 8 carbons;

alkenyl of 2 - 5 carbons;

cycloalkenyl of 5 - 8 carbons;

CO_2R^5 ;

=O , representing two substituents Q;

OH;

halogen;

$N(R^6)(R^7)$; and

$S(O)_yR^8$;

q is 0 - 4;

and

with the further provisos that:

a) two of $(Q)_qR^1$, $(Q)_qR^2$, $(Q)_qR^3$, and $(Q)_qR^4$ may be joined, and taken together with the atom(s) to which they are attached, form a spiro or nonspiro nonaromatic ring of 3 - 8 members containing 0 - 2 heteroatoms selected from the group consisting of N, O, and S;

b) at least one of R^2, R^3, and R^4 is other than H;

c) if t = 1, then T is selected from the list of substituents T above excepting alkyl, and the 4-position of the 1,3-oxazolidine ring must bear a substituent;

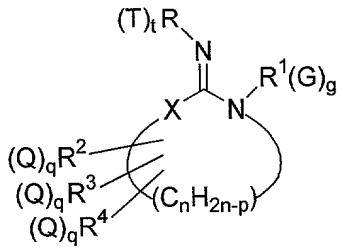
d) the sum of non-hydrogen atoms in R^1, R^2, R^3, and R^4 is at least 5;

e) when the 4-position of the 1,3-oxazolidine ring bears a carbonyl group, and R bears halogen at its 2- and 4- positions, then the 5-position of R bears H;

f) when the 4-position of the 1,3-oxazolidine ring may bear a carbonyl only if the 5-position of said ring bears at least one non-H substituent;

and pharmaceutically acceptable salts thereof.

3. (Amended) A compound having the formula



wherein

R is

substituted phenyl wherein the substituent is T; or

substituted pyridyl wherein the substituent is T;

R^1 is

alkyl of 1 - 10 carbons;

cycloalkyl of 3 - 12 carbons and containing 1 - 3 rings;

alkenyl of 2 - 10 carbons; or

cycloalkenyl of 5 - 12 carbons and containing 1 - 3 rings;

R^2, R^3, and R^4 are independently selected from the group consisting of

H;
alkyl of 1 - 10 carbons;

cycloalkyl of 3 - 12 carbons;

alkenyl of 2 - 10 carbons; and

cycloalkenyl of 5 - 12 carbons;

X is O;

n is 2;

p is the sum of non-H substituents R^2, R^3, and R^4;

T is a substituent selected from the group consisting of

alkyl of 1 - 4 carbons;

alkenyl of 2 - 4 carbons;

NO_2;

CN; and

halogen;

t is 1 - 5;

provided that when substituent moiety T is alkyl of 1 - 4 carbons, or alkenyl of 2 - 4 carbons, then T optionally may bear secondary substituents selected from the group consisting of

alkyl of 1 - 4 carbons;

alkoxy of 1 - 4 carbons;

CO_2R^5; wherein

R^5 is alkyl of 1 - 4 carbons, haloalkyl of 1 - 4 carbons, cycloalkyl of 3 - 6 carbons, or halocycloalkyl of 3 - 6 carbons;

CO_2H;

$C(O)N(R^6)(R^7)$; wherein

R^6 is H or alkyl of 1 - 5 carbons; and

R^7 is H or alkyl of 1 - 5 carbons;

CHO;

OH;

NO_2;

CN;

halogen;

$S(O)yR^8$; wherein

R^8 is alkyl of 1 - 5 carbons; and

=O;

the number of said secondary substituents being 1 or 2 with the exception of halogen, which may be employed up to the perhalo level;

G is a substituent selected from the group consisting of

halogen;

alkyl of 1 - 4 carbons;

alkenyl of 1 - 4 carbons;

cycloalkyl of 3 - 7 carbons;

cycloalkenyl of 5 - 7 carbons; and

aryl of 6 - 10 carbons;

g is 0 - 4, with the exception of halogen, which may be employed up to the perhalo level;

provided that when substituent G is alkyl of 1 - 4 carbons, alkenyl of 1 - 4 carbons, cycloalkyl of 3 - 7 carbons, or cycloalkenyl of 5 - 7 carbons, then G optionally may bear secondary substituents of halogen up to the perhalo level; and when substituent G is aryl, then G optionally may bear secondary substituents independently selected from the group consisting of alkyl of 1 - 4 carbons and halogen, the number of said secondary substituents being up to 3 for alkyl moieties, and up to the perhalo level for halogen;

Q is a substituent selected from the group consisting of

alkyl of 1 - 4 carbons;

haloalkyl of 1 - 4 carbons;

cycloalkyl of 3 - 8 carbons;

alkoxy of 1 - 8 carbons;

alkenyl of 2 - 5 carbons;

cycloalkenyl of 5 - 8 carbons; and

halogen;

q is 0 - 4;

and

with the further provisos that:

a) two of $(Q)_qR^1$, $(Q)_qR^2$, $(Q)_qR^3$, and $(Q)_qR^4$ may be joined, and taken together with the atom(s) to which they are attached, form a spiro or nonspiro nonaromatic ring of 3 - 8 members containing 0 - 2 heteroatoms selected from the group consisting of N, O, and S;

b) at least one of R^2, R^3, and R^4 is other than H;

c) if t = 1, then T is selected from the list of substituents T above excepting alkyl, and the 4-position of the 1,3-oxazolidine ring must bear a substituent;

d) the sum of non-hydrogen atoms in R^1, R^2, R^3, and R^4 is at least 5;

and pharmaceutically acceptable salts thereof.

4. canceled.

5. canceled.

7. (Amended) A pharmaceutical composition comprising a compound of claim 1, 2, 3 or 6, and a pharmaceutically acceptable carrier.

8. (Amended) A method of treating a mammal by administering to said mammal an effective amount of a compound for:

A1) enhancement of bone formation in bone weakening diseases for the treatment or prevention of osteopenia or osteoporosis;

A2) enhancement of fracture healing;

B1) use as a female contragestive agent;

B2) prevention of endometrial implantation;

B3) induction of labor;

B4) treatment of luteal deficiency;

B5) enhanced recognition and maintanence of pregnancy;

B6) counteracting of preeclampsia, eclampsia of pregnancy, and preterm labor;

B7) treatment of infertility, including promotion of spermatogenesis, induction of the acrosome reaction, maturation of oocytes, or in vitro fertilization of oocytes;

C1) treatment of dysmenorrhea;

C2) treatment of dysfunctional uterine bleeding;

C3) treatment of ovarian hyperandrogynism;

C4) treatment of ovarian hyperaldosteronism;

C5) alleviation of premenstral syndrome and of premenstral tension;

C6) alleviation of perimenstrual behavior disorders;

C7) treatment of climeracteric disturbance, including. menopause transition, mood changes, sleep disturbance, and vaginal dryness;

C8) enhancement of female sexual receptivity and male sexual receptivity;

C9) treatment of post menopausal urinary incontinence;

C10) improvement of sensory and motor functions;

C11) improvement of short term memory;

C12) alleviation of postpartum depression;

C13) treatment of genital atrophy;

C14) prevention of postsurgical adhesion formation;

C15) regulation of uterine immune function;

C16) prevention of myocardial infarction;

D1) hormone replacement;

E1) treatment of cancers, including breast cancer, uterine cancer, ovarian cancer, and endometrial cancer;

E2) treatment of endometriosis;

E3) treatment of uterine fibroids;

F1) treatment of hirsutism;

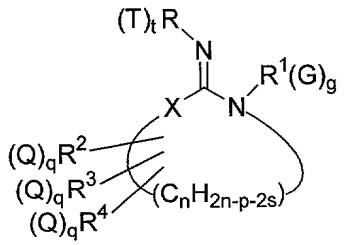
F2) inhibition of hair growth;

G1) activity as a male contraceptive;

G2) activity as an abortifacient; and

H1) promotion of mylin repair;

wherein said compound has the general formula



wherein

R is

substituted aryl of 6 - 14 carbons wherein the substituent is T; or

heteroaryl of 3 - 10 carbons and containing 1 - 3 heteroatoms selected from the group consisting of N, O, and S, with the proviso that R is other than benzofuran or benzothiophene;

R^1 is

alkyl of 1 - 10 carbons;

cycloalkyl of 3 - 12 carbons and containing 1 - 3 rings;

heterocycloalkyl of 4 - 7 carbons and containing 1 - 3 rings and 1 - 3 heteroatoms selected from the group consisting of N, O, and S;

substituted aryl of 6 - 10 carbons wherein the substituent is G;

heteroaryl of 3 - 9 carbons and containing 1 - 3 rings and 1 - 3 heteroatoms selected from the group consisting of N, O, and S;

alkenyl of 2 - 10 carbons;

cycloalkenyl of 5 - 12 carbons and containing 1 - 3 rings; or

alkynyl of 3 - 10 carbons;

R^2, R^3, and R^4 are independently selected from the group consisting of

H;

alkyl of 1 - 10 carbons;

cycloalkyl of 3 - 12 carbons;

alkenyl of 2 - 10 carbons;

cycloalkenyl of 5 - 12 carbons;

substituted aryl of 6 - 13 carbons wherein the substituent is Q;

heteroaryl of 3 - 9 carbons and containing 1 - 3 heteroatoms selected from the group consisting of N, O, and S;

CO_2R^5 ; wherein

R^5 is alkyl of 1 - 4 carbons, haloalkyl of 1 - 4 carbons, cycloalkyl of 3 - 6 carbons, or halocycloalkyl of 3 - 6 carbons;

halogen; and

=O , representing two of the groups R^2, R^3, and R^4;

X is O;

n is 2;

p is the sum of non-H substituents R^2, R^3, and R^4;

s represents the number of double bonds in the ring, and is 0, 1, or 2;

T is a substituent selected from the group consisting of

alkyl of 1 - 4 carbons;

alkoxy of 1 - 4 carbons;

aryl of 6 - 10 carbons;

CO_2H;

CO_2R^5;

alkenyl of 2 - 4 carbons;

alkynyl of 2 - 4 carbons;

$C(O)C_6H_5$;

$C(O)N(R^6)(R^7)$;wherein

R^6 is H or alkyl of 1 - 5 carbons; and

R^7 is H or alkyl of 1 - 5 carbons;

$S(O)_{y'}R^8$; wherein

y' is 1 or 2; and

R^8 is alkyl of 1 - 5 carbons;

SO_2F;

CHO;

OH;

NO_2;

CN;

halogen;

OCF_3;

N-oxide;

$O\text{-}C(R^9)_2\text{-}O$, the oxygens being connected to adjacent positions on R; and wherein

R^9 is H, halogen, or alkyl of 1 - 4 carbons;

$C(O)NHC(O)$, the carbons being connected to adjacent positions on R; and

$C(O)C_6H_4$, the carbonyl carbon and the ring carbon ortho to the carbonyl being connected to adjacent positions on R;

t is 1 - 5;

provided that when substituent moiety T is alkyl of 1 - 4 carbons; alkoxy of 1 - 4 carbons; aryl of 6 - 10 carbons; CO_2R^5; alkenyl of 2 - 4 carbons; alkynyl of 2 - 4 carbons; $C(O)C_6H_5$; $C(O)N(R^6)(R^7)$; $S(O)_yR^8$; $O\text{-}C(R^9)_2\text{-}O$, or $C(O)C_6H_4$, then T optionally may bear secondary substituents selected from the group consisting of alkyl of 1 - 4 carbons; alkoxy of 1 - 4 carbons; CO_2R^5; CO_2H; $C(O)N(R^6)(R^7)$; CHO; OH; NO_2; CN; halogen; $S(O)yR^8$; or =O, the number of said secondary substituents being 1 or 2 with the exception of halogen, which may be employed up to the perhalo level;

G is a substituent selected from the group consisting of

halogen;

OH;

OR^5;

=O , representing two substituents G;

alkyl of 1 - 4 carbons;

alkenyl of 1 - 4 carbons;

cycloalkyl of 3 - 7 carbons;

heterocycloalkyl of 3 - 5 carbons and 1 - 3 heteroatoms selected from the group consisting of N, O, and S;

cycloalkenyl of 5 - 7 carbons;

heterocycloalkenyl of 4 - 6 carbons and 1 - 3 heteroatoms selected from the group consisting of N, O, and S;

CO_2R^5;

$C(O)N(R^6)(R^7)$;

aryl of 6 - 10 carbons;

heteroaryl of 3 - 9 carbons and 1 - 3 heteroatoms selected from the group consisting of N, O, and S;

NO_2;

CN;

$S(O)_yR^8$;

SO_3R^8; and

$SO_2N(R^6)(R^7)$;

g is 0 - 4, with the exception of halogen, which may be employed up to the perhalo level;

provided that when substituent G is alkyl of 1 - 4 carbons, alkenyl of 1 - 4 carbons, cycloalkyl of 3 - 7 carbons, heterocycloalkyl of 3 - 5 carbons, cycloalkenyl of 5 - 7 carbons, or heterocycloalkenyl of 4 - 6 carbons, then G optionally may bear secondary substituents of halogen up to the perhalo level; and when substituent G is aryl or heteroaryl, then G optionally may bear secondary substituents independently selected from the group consisting of alkyl of 1 - 4 carbons and halogen, the number of said secondary substituents being up to 3 for alkyl moieties, and up to the perhalo level for halogen;

Q is a substituent selected from the group consisting of

alkyl of 1 - 4 carbons;

haloalkyl of 1 - 4 carbons;

cycloalkyl of 3 - 8 carbons;

alkoxy of 1 - 8 carbons;

alkenyl of 2 - 5 carbons;

cycloalkenyl of 5 - 8 carbons;

aryl of 6 - 10 carbons;

heteroaryl of 3 - 9 carbons and containing 1 - 3 heteroatoms selected from the group consisting of N, O, and S;

CO_2R^5

=O , representing two substituents Q;

OH;

halogen;

$N(R^6)(R^7)$;

$S(O)_yR^8$;

SO_3R^8; and

$SO_2N(R^6)(R^7)$;

q is 0 - 4

provided that when substituent Q is aryl or heteroaryl, then Q optionally may bear secondary substituents independently selected from the group consisting of alkyl of 1 - 4 carbons and halogen, the number of said secondary substituents being up to 3 for alkyl moieties and up to the perhalo level for halogen; and

with the further proviso that two of $(Q)_qR^1$, $(Q)_qR^2$, $(Q)_qR^3$, and $(Q)_qR^4$ may be joined, and taken together with the atom(s) to which they are attached, form a spiro or nonspiro nonaromatic ring of 3 - 8 members containing 0 - 2 heteroatoms selected from the group consisting of N, O, and S;

and pharmaceutically acceptable salts thereof.